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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,776	01/25/2002	Kurt Berlin	81796	9632

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EXAMINER

KIM, YOUNG J

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,776	BERLIN, KURT	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action responds the Amendment received on April 19, 2004.

Priority

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Specification

The objection to the specification for failing to comply with the Sequence Rules as set forth in 37 CFR 1.821 through 1.825, made in the Office Action mailed on October 15, 2003 is withdrawn in view of the Amendment received on April 19, 2004, fulfilling the requirements.

Claim Objections

The objection of claim 6 for minor informalities set forth in the Office Action mailed on October 15, 2003 is withdrawn in view of the Amendment received on April 19, 2004.

Claim Rejections - 35 USC § 112

The rejection of claims 2 and 10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on October 15, 2003 is withdrawn in view of the Amendment received on April 19, 2004.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite for the recitation of the phrase, "the method according to one of the preceding claims," because it is unclear to which of the above claims, claim 13 is dependent on. For the purpose of prosecution, the phrase has been assumed to mean, "the method according to *any* one of the preceding claims."

Claim Rejections - 35 USC § 102

The rejection of claims 1-3, 6, 7, 10, and 12 under 35 U.S.C. 102(a) as being anticipated by Gonzalgo et al. (WO 98/56952, published December 17, 1998), made in the Office Action mailed on October 15, 2003 is withdrawn in view of the Amendment received on April 19, 2004.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 6-10, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998).

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Gonzalzo et al. disclose a method of fluorescently detecting the methylated cytosine in a genomic DNA sample, wherein the genomic DNA is first treated with a bisulfite (page 4, line 15; claim limitation 6), the DNA amplified by PCR or polymerase chain reaction, incorporating radioactively labeled dNTPs, such as dCTP and dGTP (page 7-8; claim limitation 7), amplicons separated via electrophoresis (page 5, line 24; claim limitation 3), and the amplicons detected radioactively (page 4, lines 10-30) or fluorescently (page 8, lines 30-31; claim limitation 12). Gonzolago et al. also disclose a method of detecting the methylated cytosine, wherein the amplicons are transferred onto a nylon membrane for dot-blot analysis (page 8, lines 34-35; claim limitation 2 and 10).

Gonzalzo et al., while employing radioactively labeled dNTPs in the amplification step, do not employ fluorescently labeled dNTPs.

Gonzalzo et al. do not employ the differentially labeled fluorescently labeled NTPs comprising cy3 and cy5.

Yurov et al. disclose the use of multicolor fluorescent detection via use of cyanine dyes, more specifically cy3 and cy5 (page 391, 1st column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Gonzalzo et al. with the teachings and suggestions of Yurov et al. to arrive at the invention as claimed for the following reasons.

Although Gonzalzo et al. employ radioactively labeled dNTPs and not fluorescently labeled dNTPs, particularly cy3 and cy5 labeled dNTPs, Gonzalzo et al. acknowledges alternate ways of labeling nucleotides (*i.e.* – fluorescent labels; see page 8, lines 30-31).

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In addition to this acknowledgement, Yurov et al. disclose an explicit benefit provided by the use of cy3 and cy5 dye over the traditional fluorescent labels:

“Cyanine dyes are also useful as fluorescent labels or biological macromolecules. Cyanine 3 dye provides significantly *brigher* fluorescence than any other fluorophore, including fluorescein...” (page 391, 1st column).

Yurov et al. also disclose the advantage of using cy3 and cy5 dyes for multicolor detection assays (page 391, 2nd column).

Additionally, it is an art-recognized advantage that the use of fluorescent labels are environmentally safer as well as more efficient.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to take the suggestion of Gonzalgo et al. and the advantage offered by Yurov et al. as well as art-recognized advantage of using fluorescent labels over the radioactive labels to arrive at the claimed invention. Since the substitution of fluorescently labeled nucleotides have been well established in the art of nucleic acid amplification and detection as evidenced by Davis et al.:

“Amplified sequences can be labeled by, for example, incorporation of a labeled nucleotides (e.g., a fluorescent nucleotides such as Cy3-dUTP or Cy5-dUTP, or a radioactive nucleotide” (Davis et al., at column 19, lines 18-20)

one of ordinary skill in the art would have had a clear expectation of success at substituting the radioactive labeling with fluorescent labels provided by Yurov et al.

Applicants’ arguments received on April 19, 2004 have been fully considered but they are not found persuasive for the reasons set provided below.

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Applicants' argument regarding the use of fluorescent markers by Gonzalgo et al. being after the amplification is rendered moot in view of the present rejection.

Applicants' arguments drawn to the method of Gonzalgo et al. only permitting the analysis of a single CpG dinucleotide positions is not found persuasive as the instant method steps read on the method of Gonzalgo et al. in view of the obviousness reasoning set forth above.

Applicants' arguments drawn to the hybridization of the "amplificate" [*sic*] to an oligonucleotide is also not found persuasive because Yurove et al. as well as Davis et al. discusses the hybridization of the amplicons to an array of immobilized oligonucleotides (for example, *Davis et al.*, column 19, lines 28-30).

Therefore, the invention as claimed is obvious over the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending

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Application No. 10/220,090. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-13 are drawn to a method involving the steps of chemically treating a genomic DNA with a reagent, wherein said reagent is bisulfite, followed by the amplification with fluorescently labeled nucleotides, specifically dCTP or dGTP, separation of the labeled amplified products from the remains, followed by their detection. Some embodiments are drawn to the method of separating the labeled amplified products, such as capillary gel electrophoresis, HPLC.

Claims 1-29 of the '090 application are also drawn to a method involving the steps of treating a genomic DNA with a reagent, wherein said reagent (claim 1-a), amplifying the treated genomic DNA (claim 1-b), separating the amplified product (claim 1-c), and followed by their detection (claim 1-d), wherein the specific reagent contemplated is bisulfite [0033, 0056, claim 8], and wherein the labels are recited as being Cy3-dCTP or Cy5-dCTP, which allows the detection of methylations of cytosine bases. Claims 14-16, also recite alternative method of separation/detection method such as mass spectrometry.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 10/220,896. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

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Claims 1-13 are drawn to a method involving the steps of chemically treating a genomic DNA with a reagent, wherein said reagent is bisulfite, followed by the amplification with fluorescently labeled nucleotides, specifically dCTP or dGTP, separation of the labeled amplified products from the remains, followed by their detection. Some embodiments are drawn to the method of separating the labeled amplified products, such as capillary gel electrophoresis, HPLC.

Claims 1-26 of the '0896 application are also drawn to a method involving the steps of treating a genomic DNA with a reagent, wherein said reagent (claim 1-a), amplifying the treated genomic DNA (claim 1-b), separating the amplified product (claim 1-c), and followed by their detection (claim 1-d), wherein the specific reagent contemplated is bisulfite [0033, 0053, claim 9], and wherein the labels are recited as being Cy3-dCTP or Cy5-dCTP, which allows the detection of methylations of cytosine bases [0012]. Claims 14-19, also recite alternative method of separation/detection method such as mass spectrometry.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

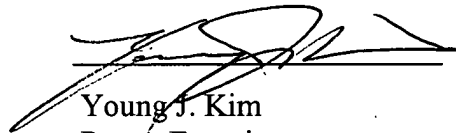
No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the

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Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (517) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0507.



Young J. Kim
Patent Examiner
Art Unit 1637
7/19/04

yjk